Bioorganic & Medicinal Chemistry Letters 18 (2008) 4929–4931

Contents lists available at ScienceDirect

Bioorganic & Medicinal Chemistry Letters

journal homepage: www.elsevier.com/locate/bmcl

Synthesis and activity of 1-(3-amino-1-phenylpropyl)indolin-2-ones: A new class of selective norepinephrine reuptake inhibitors

Casey C. McComas [a,*], An T. Vu [a], Paige E. Mahaney [a], Stephen T. Cohn [a], Andrew Fensome [a], Michael A. Marella [a], Lisa Nogle [a], Eugene J. Trybulski [a], Fei Ye [a], Puwen Zhang [a], Peter Alfinito [b], Jenifer Bray [b], Grace Johnston [b], Elizabeth Koury [b], Darlene C. Deecher [b]

[a] Chemical and Screening Sciences, Wyeth Research, 500 Arcola Road, S2227A, Collegeville, PA 19426, USA
[b] Women's Health and Musculoskeletal Biology, Wyeth Research, 500 Arcola Road, Collegeville, PA 19426, USA

ARTICLE INFO

Article history:
Received 30 July 2008
Revised 14 August 2008
Accepted 18 August 2008
Available online 22 August 2008

This manuscript is dedicated to the memory of Dr. Ronald L. Magolda.

ABSTRACT

Norepinephrine and serotonin play an important role in a wide variety of biological processes and are implicated in a number of neurological disorders. A novel class of 1-(3-amino-1-phenylpropyl)indolin-2-ones was designed and synthesized that displays potent norepinephrine reuptake inhibition while maintaining high selectivity (>100-fold) against the human serotonin and dopamine transporters.

Norepinephrine (NE), serotonin (5-HT), and dopamine (DA) are essential monoamine neurotransmitters in both the central and peripheral nervous system and are involved in regulation of a wide variety of physiological functions.[1] There are a number of neurological disorders thought to be associated with monoamine neurotransmitter deficiency thus making this system an important target for drug development.

Selective serotonin reuptake inhibitors (SSRIs) such as fluoxetine (**1**), paroxetine (**2**), and sertraline have been used extensively to treat depression (Fig. 1). More recently, considerable research has focused on development of compounds that include both the inhibition of serotonin and norepinephrine reuptake.[2,3] These efforts have led to the development of compounds such as duloxetine (**3**), which is a potent serotonin and norepinephrine reuptake inhibitor (Table 1).

Duloxetine is marketed for major depressive disorder (MDD) and shows efficacy in the treatment of chronic pain disorders and stress urinary incontinence (SUI).[4] Desvenlafaxine also inhibits the reuptake of both serotonin and norepinephrine and is approved for the treatment of MDD.[5] Alternatively, selective norepinephrine reuptake inhibitors, such as atomoxetine (**4**), nisoxetine (**5**), and reboxetine (**6**) have been developed for the treatment of MDD and attention deficit hyperactivity disorder (ADHD).[6,7] These compounds show selectivity ratios ranging from 16 for atomoxetine (**4**) to 81 for reboxetine (**6**).

Norepinephrine reuptake inhibitors (NRIs) exert their effects by binding to the norepinephrine transporter (NET) protein located presynaptically. This binding interaction results in an increase in the extracellular concentration of NE in the synaptic cleft resulting in increased downstream cellular signaling.[8] Neurological disorders such as depression, pain, and vasomotor symptoms are thought to result from fluctuations in the levels of 5-HT and NE in the brain and in particular the cortical, hippocampal and hypothalamic regions. Our interest in understanding the role of NE in these disorders led us to undertake a program to develop selective NE reuptake inhibitors (NRIs). Previously we disclosed a series of 3-(1*H*-indol-1-yl)-3-arylpropan-1-amines (**7**) that displayed dual acting NE and 5-HT reuptake inhibition.[9] In an effort to improve the chemical stability of this series we designed a 1-(3-amino-1-phenylpropyl)indolin-2-one scaffold leading to compounds with the core structure **8** (Fig. 2). The use of an indolin-2-one headpiece offered the additional advantage of greater versatility with respect

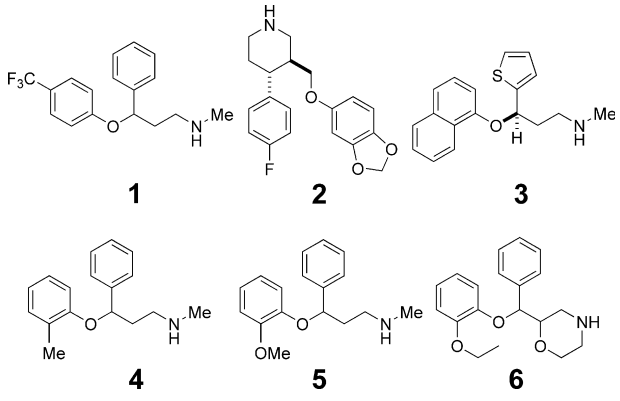

Figure 1.

* Corresponding author. Tel.: +1 484 865 8724; fax: +1 484 865 9398.
E-mail address: mccomac@wyeth.com (C.C. McComas).

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doi:10.1016/j.bmcl.2008.08.060

Table 1
Inhibition of monoamine reuptake at the hNET and hSERT of compounds within the aryloxypropanamine class

Compound	hNET IC_{50}[a] (nM)	hSERT IC_{50}[b] (nM)	hSERT IC_{50}/hNET IC_{50}[c]
Fluoxetine (**1**)	563	10	0.02
Paroxetine (**2**)	100	2	0.02
(*S*)-Duloxetine (**3**)	4	3	0.75
Atomoxetine (**4**)	3	48	16
Nisoxetine (**5**)	6	277	46
Reboxetine (**6**)	3	242	81

[a] Inhibition of norepinephrine uptake in MDCK-Net6 cells, stably transfected with human NET.
[b] Inhibition of serotonin uptake in JAR cells, stably transfected with human SERT.
[c] Unitless value as a ratio in which higher numbers represent relatively greater NET selectivity.

to substitution at the 3-position of the heterocycle. Introduction of an indolin-2-one revealed a dramatic effect of functionality about the 2 and 3 position of the heterocycle on NE selectivity and led to the discovery of a new series of 1-(3-amino-1-phenylpropyl)indolin-2-ones which are potent and selective NRIs.

Initially, a racemic synthesis of 1-(3-amino-1-phenylpropyl)indolin-2-ones (Scheme 1) was developed. Alkylation of oxindole at the 3-position provided **10** followed by N-alkylation with benzyl bromide to generate **11**. Installation of an ethanol sidechain was accomplished by treatment with butyllithium and (2-bromoethoxy)-*t*-butyl-dimethyl-silane followed by removal of the silyl group with TBAF. At this stage the racemic mixture of alcohols was resolved by preparative chiral HPLC to give enantiomers **12** and **13**. Alcohol **13** was then converted to the tosylate which was displaced with methylamine to give 1-(3-amino-1-phenylpropyl)indolin-2-one **(*R*)-14a**. Alcohol **12** was treated in a similar manner to give the enantiomeric 1-(3-amino-1-phenylpropyl)indolin-2-one **(*S*)-18a**.

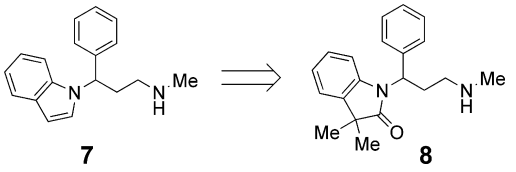
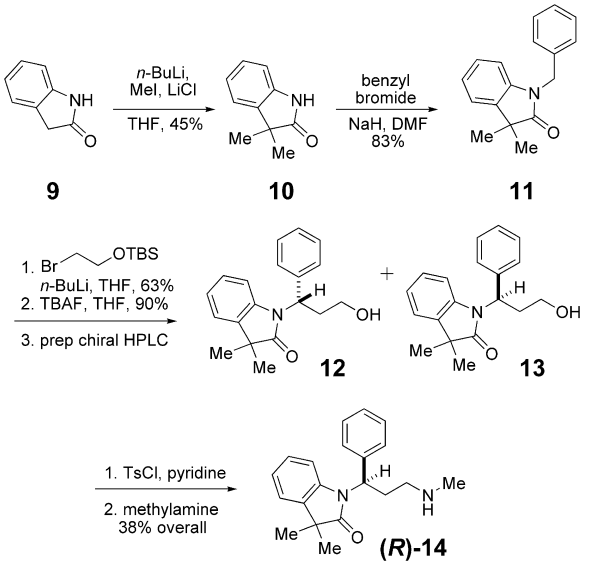


Figure 2. 1-(3-amino-1-phenylproplyl)indolin-2-ones.

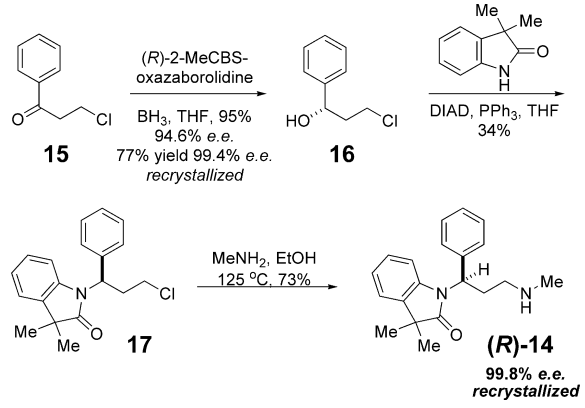


Scheme 1. Synthesis of 1-(3-amino-1-phenylproplyl)indolin-2-ones.

An enantioselective synthesis was designed in order to assign the stereochemistry at the benzylic position and eliminate the need for an HPLC resolution step (Scheme 2). Reduction of 3-chloro-1-phenylpropan-1-one (**15**) with BH_3 in the presence of catalytic (*R*)-2-methyl-CBS-oxazaborolidine provided the (*S*)-alcohol in 94.6% *e.e.* which could be recrystallized to give **16** in 99.4% *e.e.* and 77% yield. The alcohol was displaced with 3,3-dimethyloxindole under Mitsunobu conditions to generate **17**. This reaction proceeded with clean inversion of stereochemistry with no observed racemization. Finally, substitution of the chloride with methylamine yielded 1-(3-amino-1-phenylpropyl)-indolin-2-one **(*R*)-14a** in >99.8% *e.e.* after recrystallization of the HCl salt. Either enantiomer of 1-(3-amino-1-phenylpropyl)-indolin-2-one could be accessed by this route depending on the isomer of the CBS catalyst used.

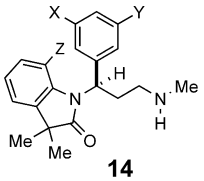
Compounds **14, 18, 19,** and **20** were evaluated in vitro for the ability to inhibit both the uptake of NE in MDCK-Net6 cells stably transfected with human NET and 5-HT in JAR cells stably transfected with the human serotonin transporter (hSERT). Selected compounds were then assayed for inhibition of radioligand binding to the human dopamine transporter (hDAT). The experimental methods for these biochemical assays have been detailed previously.[10] The results of these studies are summarized in Table 2.

The promise of this series was immediately apparent upon evaluation of the unsubstituted analog **14a** that showed moderate hNET potency but was highly selective against hSERT. The enantiomeric compound **18a** was only weakly active and revealed the strong eutomer/distomer property of this series. Encouraged by this result, the nitrogen R-group was varied but even minor changes resulted in a loss of activity. Previous SAR indicated that fluorination of the 7-position of the heterocyclic ring and the 3-position of the pendant aryl ring improved activity.[11] Following this observed trend, synthesis of **14b** and **14c** led to greater than 10-fold improvement in hNET potency while maintaining excellent selectivity over hSERT (selectivity ratio of 182 and >157, respectively). Addition of chlorine to the pendant aryl ring (**14d** and **14e**) led to a 2-fold increase in hNET activity but also led to approximately a 10-fold increase in hSERT potency. Addition of a second fluorine to the aryl ring (**14f**) showed the same improvement in activity (7 nM) while maintaining high selectivity over hSERT (selectivity ratio 192). Expansion of the gem-dimethyl group to a spirocyclohexyl group at the 3,3-position of the oxindole was briefly explored. Compounds **19a** and **19b** demonstrated that an increase in steric bulk about the 3-position of the heterocycle was well tolerated and even showed a modest improvement in potency. The *S*-enantiomers (**20a** and **20b**) also showed the same



Scheme 2. Enantioselective synthesis of 1-(3-amino-1-phenylproplyl)indolin-2-ones.

Table 2
Characterization of compounds 14, 18, 19, and 20 at the human norepinephrine, serotonin, and dopamine transporters



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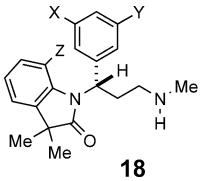

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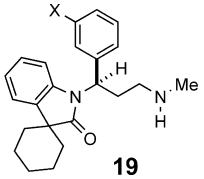

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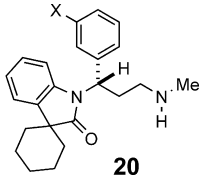

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Compound	X	Y	Z	hNET IC_{50}[a] (nM)	hSERT IC_{50}[b] (nM)	hSERT IC_{50}/hNET IC_{50}[c]	hDAT % inhib @ 1 μM
7	H	H	H	47	327	7	44%
14a	H	H	F	175	>3000	>17	3%
14b	F	H	F	14	2550	182	7%
14c	F	Cl	F	19	>3000	>157	0%
14d	H	Cl	F	7	290	41	10%
14e	F	F	F	6	330	55	0%
14f	H	H	H	7	1350	192	0%
18a	H			>3000	1950	<0.65	3%
19a	F			26	>3000	>115	20%
19b	H			53	>3000	>56	26%
20a	F			>3000	1150	<0.38	1%
20b				>3000	1750	<0.58	0%

[a] Inhibition of norepinephrine uptake in MDCK-Net6 cells, stably transfected with human NET. Desipramine (IC_{50} = 3.9 ± 0.5 nM) was used as standard.
[b] Inhibition of serotonin uptake in JAR cells, stably transfected with human SERT. Fluoxetine (IC_{50} = 10.3 ± 1.7 nM) was used as a standard.
[c] Unitless value as a ratio in which higher numbers represent relatively greater NET selectivity.

loss of hNET activity observed previously and even displayed a modest selectivity for hSERT. Although not anticipated to be active at DAT, these compounds were evaluated for their dopamine transporter binding activity and showed very weak affinity for the DA transporter. In general compounds **14** and **19** were potent NRIs and showed excellent selectivity against the 5-HT and DA trasporters.

In summary, a medicinal chemistry program focused on the design of potent and selective NRIs successfully identified a new class of a 1-(3-amino-1-phenylpropyl)indolin-2-ones that represent some of the most selective hNET ligands reported to date. Compounds **14d**, **14e**, and **14f** in particular, showed excellent potency at the hNET and remarkable selectivity over hSERT and hDAT. Additionally, compounds **14d**, **14e**, and **14f** have low TPSA (~32) and are therefore anticipated to cross the blood-brain barrier efficiently.[12] These compounds will be further profiled in in vivo models of neurological disorders and dysfunction thought to be associated with NE deficiency. The synthesis and characterization of additional compounds is ongoing in an effort to identify potent and selective NRIs that may have utility in treating various neurological disorders.

Acknowledgments

The authors thank the members of the Discovery Analytical Chemistry group at Wyeth, especially Diane Andraka, Scott Brecker, Rebecca Dooley, Dr. Christopher Petucci, and Dr. Oliver McConnell for compound analysis. We also thank Dr. Ron Magolda and Dr. Magid Abou-Gharbia for their encouragement and support.

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